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Gemfibrozil, Nicotinic Acid and Combination Therapy in Patients With Isolated Hypoalphalipoproteinemia: A Randomized, Open-Label, Crossover Study

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OBJECTIVES To assess the effects of nicotinic acid (NA), gemfibrozil and combination therapy on the lipid profile of patients with clinical atherosclerotic disease and isolated hypoalphalipoproteinemia.

BACKGROUND Isolated hypoalphalipoproteinemia (low high density lipoprotein cholesterol [HDL-C] alone) accounts for a significant percentage of patients with premature atherosclerosis. However, it remains unclear whether currently available pharmacotherapy has the ability to favorably affect the lipid profile and therefore potentially reduce clinical events.

METHODS Twenty-three patients with clinically well-defined atherosclerosis and isolated hypoalphalipoproteinemia were prospectively randomized to receive gemfibrozil, NA or combination therapy in an open-label, crossover design trial to assess the effects on serum lipids. Lipid profiles and other relevant laboratory variables were monitored while the patients were on and off pharmacologic lipid-modulating therapy.

RESULTS In those 14 patients able to tolerate all forms of pharmacotherapy, HDL-C of 0.89 ± 0.17 mmol/liter (34.5 ± 6.5 mg/dl) increased by 15%, to 1.02 ± 0.18 mmol/liter (39.7 ± 7.1 mg/dl), while taking gemfibrozil (1200 mg/day); by 35%, to 1.20 ± 0.21 mmol/liter (46.5 ± 8.1 mg/dl), while taking NA (mean dose 2,250 mg/day); and by 45%, to 1.29 ± 0.19 mmol/liter (50.0 ± 7.5 mg/dl), while taking combination therapy of gemfibrozil plus NA ($p < 0.001$ for all interventions as compared with baseline/washout; $p < 0.005$ NA vs. gemfibrozil; $p < 0.001$ combination therapy vs. gemfibrozil alone; $p = 0.088$ combination therapy vs. NA alone). Statistically significant favorable alterations were also observed with low density lipoprotein cholesterol (LDL-C), LDL-C/HDL-C, non-HDL-C/HDL-C, apolipoprotein (Apo) B and Apo B/Apo A1.

CONCLUSIONS In the majority of patients with clinical atherosclerotic disease and isolated hypoalphalipoproteinemia, pharmacologic therapy to raise HDL-C is not only feasible but is also effective with currently available agents, particularly when used in combination. (J Am Coll Cardiol 2000; 35:640–6) © 2000 by the American College of Cardiology

In the decade since the first published results of the Honolulu (1), Framingham (2) and Tromso (3) studies, the independent, strong, inverse relation between levels of high density lipoprotein cholesterol (HDL-C) and coronary artery disease (CAD) has been confirmed, with a few exceptions according to epidemiologic studies in several countries (4–11). Although low levels of HDL-C are often associated with elevated levels of plasma triglycerides or low density lipoprotein cholesterol (LDL-C), or both (12–14), primary hypoalphalipoproteinemia in non-obese, nonsmoking and regularly exercising individuals has been well documented (15,16), may be familial (17) and is associated with the development of premature clinical CAD (17,18). Indeed, of those patients undergoing diagnostic coronary arteriography, between 4% and 19% have been shown to have hypoalphalipoproteinemia, as defined earlier, as their sole lipid abnormality (16–19). Although the Helsinki heart study showed a decrease in CAD risk that appeared to be associated with a pharmacologically induced increase in HDL-C, the results were limited to patients with moderate to high levels of LDL and very low density lipoprotein cholesterol (VLDL-C) combined. No clinical end point trial has yet been published that specifically targets patients with isolated low levels of HDL-C for intervention. A seemingly necessary prerequisite for cardiac event reduction

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Abbreviations and Acronyms

Apo A1	=	apolipoprotein A1
Apo B	=	apolipoprotein B
CAD	=	coronary artery disease
HDL-C	=	high density lipoprotein cholesterol
LDL-C	=	low density lipoprotein cholesterol
NA	=	nicotinic acid
NCEP	=	National Cholesterol Education Program
TC	=	total cholesterol
VA-HIT	=	High-density-lipoprotein Intervention Trial of the Department of Veterans Affairs
VLDL-C	=	very low density lipoprotein cholesterol

in this patient group, however, would seem to be a significant increase in HDL-C by the intervention under study.

The present report was a randomized, controlled, open-label, crossover trial of gemfibrozil, nicotinic acid (NA) and combination gemfibrozil plus a maximally tolerated dose of NA in patients with primary hypoalphalipoproteinemia, all of whom had documented atherosclerotic vascular disease, to assess the effect of these agents on the lipid profile. Secondarily, safety and tolerability of individual therapies in this small group of patients were also examined.

METHODS

Patient group. Twenty-six adult patients with atherosclerotic vascular disease who had already been stabilized by step 2 of the National Cholesterol Education Program (NCEP) diet and had total cholesterol (TC) <220 mg/dl, LDL-C <160 mg/dl, HDL-C <40 mg/dl and triglycerides <200 mg/dl on two consecutive lipid profiles within two months of study entry were deemed eligible for study. These values were chosen to define isolated hypoalphalipoproteinemia based on previously published studies (20,21). During screening, patients were excluded if they had diabetes mellitus, gouty arthritis, abnormal liver function, thyroid disease, psychiatric illness, drug or alcohol abuse or if they were undergoing treatment with lipid-lowering agents, anticonvulsant agents or corticosteroids.

Twenty-three patients (22 men and 1 woman, 41 to 80 years old [mean 61]), many of whom were enrolled in a maintenance exercise cardiac rehabilitation program, freely agreed to participate and were randomly assigned to study medications. Twenty-two patients had a history of CAD (17 with S/P remote myocardial infarction, three with S/P remote coronary artery bypass graft surgery and two with chronic stable angina) and one had proven peripheral vascular disease. Body mass index was 26 ± 3 kg/m^2. All patients either were nonsmokers or had quit smoking over three months before study enrollment. Patients taking a variety of cardiovascular drugs for control of angina, hypertension or congestive heart failure were allowed to participate only if they maintained the same dosage regimen throughout the entire study, with two exceptions: One patient discontinued dyazide after the initial dietary run-in phase before drug randomization and another had furosemide added for the treatment of peripheral edema while taking NA therapy.

Treatment protocol. Patients were initially screened by laboratory assessment and physical examination. All patients had previously been placed on an isocaloric saturated fat/cholesterol-restricted NCEP step 2 maintenance diet (22) by a registered dietician for a minimum of 12 weeks. Compliance with the diet throughout the entire study period was established by taking once a month three-day dietary histories, the data from which were entered by the dietician into a standard software computer analysis program (Nutritionist III, N-Squared Computing, Silverton, Oregon). Patients were seen in the office at least every 12 weeks, at which time they were interviewed and recounseled regarding dietary and drug adherence to the program, maintenance of body weight and level of exercise habit.

Patients who met the inclusion criteria were randomized to receive either open-label drug with gemfibrozil, 600 mg orally twice a day, or immediate-release crystalline NA, 100 to 250 mg orally three times a day, with meals. The first patient was randomized to gemfibrozil, the second to NA and so forth. For gemfibrozil, 600 mg twice a day is both the recommended initial and maximal dose. For NA, the dose was gradually increased, initially to 1,500 mg/day and subsequently to the maximally tolerated dose, not to exceed 3,000 mg/day. On completion of three months of maximal dosing with either agent, or sooner if intolerant to therapy, the patient was subsequently crossed over to the other treatment arm. If the patient was able to tolerate both gemfibrozil and NA individually, combination therapy with gemfibrozil, 600 mg orally twice a day, and the previous maximally tolerated dose of NA was administered for an additional three-month period. After completion of the active drug portion of the study, all pharmacologic lipid-lowering therapy was discontinued, and three months later a pair of control sera was obtained one week apart for lipid analysis. These values were averaged with the pretreatment eligibility lipid profiles to derive the baseline values (Table 1). During the run-in phase and at the end of each drug treatment phase, blood for routine hematologic liver function, creatine kinase and a minimum of two samples at weekly intervals for lipid and apolipoprotein (Apo) levels were drawn and analyzed.

Lipid analyses. Lipid profiles, Apo B and Apo A1 concentrations were measured at Roche Laboratories (Nutley, New Jersey). Total serum cholesterol was measured enzymatically with an analyzer (Olympus-AU 5000, Melville, New York) with a coefficient of variation of 1.6% (data provided by Roche Laboratories). The HDL-C levels were determined by fractionating with manganese and dextran followed by centrifugation. The HDL containing superna-

Table 1. Comparison of Responses to Gemfibrozil, Nicotinic Acid and Combination Pharmacotherapy in Patients (n = 14) With Isolated Hypoalphalipoproteinemia

	Baseline	Gemfibrozil	Nicotinic Acid	Combined Therapy
Level in mmol/liter (mg/dl)				
Total cholesterol	4.87 ± 0.69 (189 ± 27)	4.49 ± 0.70 (174 ± 27)*	4.33 ± 0.74 (168 ± 29)*	3.91 ± 0.76 (152 ± 29)*†‡
LDL-C	3.40 ± 0.60 (132 ± 23)	3.06 ± 0.64 (119 ± 25)*	2.67 ± 0.64 (104 ± 25)*†	2.33 ± 0.72 (91 ± 28)*†‡
HDL-C	0.89 ± 0.17 (35 ± 7)	1.02 ± 0.18 (40 ± 7)*	1.20 ± 0.21 (47 ± 8)*†	1.29 ± 0.19 (50 ± 8)*†
Triglycerides	1.28 ± 0.43 (113 ± 38)	0.87 ± 0.45 (78 ± 40)*	1.02 ± 0.58 (91 ± 52)	0.65 ± 0.22 (58 ± 20)*
Apo B	2.31 ± 0.51 (90 ± 20)	1.94 ± 0.42 (75 ± 16)†	1.69 ± 0.51 (66 ± 20)*†	1.51 ± 0.54 (59 ± 21)*†
Apo A1	2.97 ± 0.44 (115 ± 17)	3.14 ± 0.36 (122 ± 14)	3.38 ± 0.36 (131 ± 14)	3.58 ± 0.56 (139 ± 22)*†
Ratio				
LDL-C/HDL-C	3.9 ± 0.9	3.1 ± 0.9*	2.3 ± 0.9*†	1.9 ± 0.7*†‡
Non–HDL-C/HDL-C	4.6 ± 1.2	3.5 ± 1.1*	2.8 ± 1.1*	2.1 ± 0.8*†‡
Apo B/Apo A1	0.82 ± 0.21	0.63 ± 0.11	0.53 ± 0.16*	0.43 ± 0.13*†

*Significantly different from baseline. †Significantly different from gemfibrozil. ‡Significantly different from nicotinic acid. Data are presented as the mean value ± SD.
Apo = apolipoprotein; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TC = total cholesterol.

tant was assayed for cholesterol by an enzymatic chromophobic technique (American Monitor, KDA Analyzer) with a coefficient of variation of 4.1% (data provided by Roche Laboratories). Triglyceride levels were measured enzymatically with an Olympus-AU 5000 analyzer with a coefficient of variation of 2.4% (data provided by Roche Laboratories). The VLDL-C levels were estimated by dividing the triglycerides by 5, as described by Friedewald et al. (23). Non–HDL-C was calculated by subtracting the measured HDL-C from the measured TC. LDL-C was calculated by subtracting VLDL-C and HDL-C from TC. Apolipoproteins A1 and B were measured in sera using immunonephelometry with a Cobas Bio centrifugal analyzer and antibodies against human Apo A1 and Apo B provided by Reagents Applications, Inc. (San Diego, California).

Statistical analysis. Single-factor repeated measures analysis of variance (ANOVA) (24) was performed to assess differences between the four study phases (dietary alone [baseline plus follow-up washout], diet plus gemfibrozil, diet plus NA and diet plus gemfibrozil plus NA). Lipid values after the dietary run-in phase and after drug washout were combined and presented as baseline to attempt to minimize regression to the mean (25). Statistical comparisons with baseline were performed in 21, 17 and 14 patients who were able to tolerate gemfibrozil, some dose of NA and combination gemfibrozil plus NA. When the *F* statistic by ANOVA was significant (alpha 0.05), multiple comparisons were made using the paired two-tailed *t* test with the Bonferroni correction to adjust for multiplicity of testing. Six comparisons were made, and significance was defined at an alpha value of 0.05/6, or 0.0083, or lower.

RESULTS

The baseline characteristics of the patients before randomization are shown in Table 2. Throughout the course of the study, body weight change, by design, was minimal (mean −0.8 lb [range −9.0 to +9.3]), which represented only 0.5% (range −6.5% to 4.1%) of baseline. Patients remained compliant with the low cholesterol–low fat diet (average cholesterol 167 ± 27 mg/day; 22.0 ± 5.3 calories derived from fat with a polyunsaturated, saturated, monosaturated fat ratio of 1.0:1.4:1.4) throughout the entire study period. The effects of gemfibrozil or NA individually on the lipid profile in the 21 and 17 patients, respectively, who tolerated these agents as monotherapy did not differ from the lipid profile of the 14 patients who were able to tolerate combination therapy. As such, only data from the final group of patients (n = 14) who were able to tolerate gemfibrozil, low or high dose NA and combination gemfibrozil plus NA for the entire study period are presented (Table 1). The values displayed for NA are derived from the highest tolerated dose in a given patient.

On gemfibrozil monotherapy, two patients discontinued active drug therapy—one because of nausea and the other because of asthenia—before follow-up lipid studies were performed. Gemfibrozil decreased triglycerides by 31% and LDL-C by 10% and increased HDL-C by 15% in comparison with baseline. A significant inverse correlation (p =

Table 2. Baseline Characteristics of Patients (n = 23) With Isolated Low High Density Lipoprotein Cholesterol Before Randomization

Age (yrs)	60.9 ± 11.5
Gender (M/F)	22/1
Diagnosis	22 CAD, 1 PVD
Weight (lb)	177.9 ± 28.1
BMI (kg/m^2)	26.0 ± 3.0
Level in mmol/liter (mg/dl)	
Total cholesterol	4.90 ± 0.62 (190.4 ± 24.2)
LDL-C	3.38 ± 0.51 (131.3 ± 19.6)
HDL-C	0.86 ± 0.14 (33.3 ± 5.6)
Triglycerides	1.46 ± 0.53 (129.6 ± 47.8)
Apo A1	2.93 ± 0.35 (113.5 ± 13.7)
Apo B	2.36 ± 0.47 (91.4 ± 18.1)

Data are presented as the mean value ± SD or number of patients.
BMI = body mass index; CAD = coronary artery disease; PVD = peripheral vascular disease; other abbreviations as in Table 1.

0.014 for the group correlation coefficient) was noted between the decrease in triglycerides and the increase in HDL-C ($r = -0.63$). The LDL-C/HDL-C and non–HDL-C/HDL-C ratios were significantly decreased by 21% and 24%, respectively.

Twenty-three patients were initially treated with immediate-release crystalline niacin, and six patients experiencing severe flushing were subsequently treated with slow-release NA. On low dose NA (mean dose 1,400 mg/day [range 1,000 to 1,500]), six patients experienced one or more side effects necessitating withdrawal from therapy. Two subjects had an attack of gout, two had urticaria, two had a pruritic macular rash, one had nausea and one had asymptomatic transaminasemia. In comparison with baseline, low dose NA decreased LDL-C by 14% and increased HDL-C by 26%. The LDL-C/HDL-C and non–HDL-C/HDL-C ratios were both decreased by 29%, consistent with a lack of triglyceride lowering on low dose NA. The Apo B/Apo A1 ratio decreased by 13%.

Seventeen patients who tolerated low dose NA were advanced to high dose NA (mean dose 2,250 mg/day [range 2,000 to 3,000]). Fourteen patients were treated with immediate-release crystalline niacin and three with slow-release NA. On high dose NA, four patients experienced one or more side effects necessitating withdrawal from therapy. Three subjects had severe nausea, one had dizziness, one had myalgias and two had asymptomatic transaminasemia. In comparison with baseline, high dose NA significantly decreased LDL-C and Apo B by 22% and 27%, respectively, and increased HDL-C by 35%. No significant correlation ($p = 0.126$ for the group correlation coefficient) was noted between the 20% decrease in triglycerides and the increase in HDL-C ($r = -0.43$). The LDL-C/HDL-C, non–HDL-C/HDL-C and Apo B/Apo A1 ratios were significantly decreased by 41%, 39% and 35%, respectively.

Fifteen patients underwent combined therapy with gemfibrozil and the highest dose of NA, which previously had been tolerated as monotherapy. Ten patients were treated with immediate-release crystalline niacin and five with slow-release NA. On combination lipid-lowering therapy, one patient who had previously experienced only mild nausea on gemfibrozil now had severe nausea, which resolved on discontinuation of gemfibrozil. No patient had myalgias or myositis. Combination therapy in 14 patients significantly decreased LDL-C by 31%, 24% and 13% in comparison with baseline, gemfibrozil and the previous maximally tolerated dose of NA, respectively. Apo B was significantly decreased by 35% and 22% in comparison with baseline and gemfibrozil monotherapy, respectively. HDL-C and Apo A1 were significantly increased by 45% and 21%, respectively, and by 26% and 14% in comparison with baseline and gemfibrozil monotherapy, respectively. LDL-C/HDL-C was significantly reduced by 51%, 39% and 17% in comparison with baseline, gemfibrozil and the previous maximally tolerated dose of NA, respectively. Non–HDL-C/HDL-C was significantly reduced by 54%, 40% and 25% in comparison with baseline, gemfibrozil and the previous maximally tolerated dose of NA, respectively. Apo B/Apo A1 was significantly decreased by 48% and 32% in comparison with baseline and gemfibrozil monotherapy, respectively.

DISCUSSION

It is clear from multiple angiographic (26–30) as well as clinical outcome trials (31–34) that LDL-C is a potent risk factor for the development of atherosclerotic CAD and that pharmacologic therapy designed to lower LDL-C in certain high risk patient groups results in slower progression of atherosclerotic disease as well as a reduction in both fatal and nonfatal myocardial infarctions. That such therapy is capable of reducing but not eliminating further progression of the atherosclerotic process is consistent with the known multifactorial nature of this disease and the presence of other significant dyslipidemias in this patient group (18,19,35,36). Paramount among these dyslipidemias are disorders associated with a low HDL-C, a lipoprotein closely associated with reverse cholesterol transport (37,38) and a known independent inverse risk factor for the development of atherosclerotic heart disease (39). Until recently, however, evidence to suggest that drug therapy which can increase HDL-C may be associated with decreased cardiac morbid events was quite limited (40,41) and confined to those patients with significant mixed hyperlipidemia (i.e., increased LDL-C and triglycerides) in whom there had been a concomitant reduction of LDL-C and triglycerides (42,43). With the recent publication of the large secondary prevention High-density lipoprotein cholesterol Intervention Trial of the Department of Veterans Affairs (VA-HIT) (44), however, it is now clear that a meaningful reduction in the risk of future major cardiovascular events is possible in patients with hypoalphalipoproteinemia, perhaps by raising HDL-C without lowering LDL-C.

In the current study, patient acceptance of gemfibrozil was quite high (91% [21 of 23 patients]) and was associated with a modest increase in HDL-C and a major decrease in triglycerides. Although the increase in HDL-C that we found somewhat exceeds that reported by some investigators (44–46), it is similar to that described by others (47) and also to that associated with the use of reductase inhibitors in comparable patient groups (46,48). In the current series of normotriglyceridemic subjects, the rise in HDL-C with the use of gemfibrozil was inversely related to the fall in triglycerides, as previously reported in patients with hypertriglyceridemia (45,49,50). Like previously reported series of patients with isolated hypoalphalipoproteinemia (45,46), the increase in HDL-C was not associated with any increase in Apo A1. This is in contrast to the increase in Apo A1 seen in patients with phenotypic type IV hyperlipoproteinemia treated with gemfibrozil (50,51).

In the current study, 6 (26%) of 23 patients and an additional 4 (17%) of 23 patients were unable to tolerate at least three months of low dose or high dose NA therapy, respectively. This is similar to the 36% to 40% rate of intolerance reported in other prospective clinical trials in which crystalline NA was used (21,52). As reported previously (21,53), most of the increase in HDL-C and Apo A1 can be accomplished by relatively low dose NA therapy. In the current study, high dose NA (mean 2,250 mg/day) was associated with a 35% and 13% increase in HDL-C and Apo A1, respectively—values in good agreement with those previously reported in patients with isolated hypoalphalipoproteinemia treated similarly (21,52). In the current study, unlike gemfibrozil, there was no clear relation between the amount of HDL-C increase and triglyerides decrease in patients treated with NA. A similar finding was reported in two previous series employing sustained-release NA preparations in similar patient groups (20,53). Use of high dose NA in the current study was associated with a 22% and 27% reduction in LDL-C and Apo B, respectively—with these decrements following a more linear dose response. These results are again consistent with the 14% to 18% and 21% to 32% reduction in LDL-C and Apo B, respectively, previously reported in somewhat similar patients (21,52).

To our knowledge, this is the first study, in the same group of patients with isolated hypoalphalipoproteinemia, to address the question of combination gemfibrozil and NA therapy with regard to the effects on blood lipids. With combination therapy, LDL-C, Apo B and triglycerides were reduced by 31%, 35% and 49%, respectively, with the LDL-C reduction being greater than that while using gemfibrozil or NA alone. With combination therapy, HDL-C was increased by 45% over baseline and significantly further when compared with gemfibrozil alone. LDL-C/HDL-C, non–HDL-C/HDL-C and Apo B/Apo A1 were reduced by 51%, 54% and 48%, respectively—each of these reductions being greater than that while using gemfibrozil or NA alone. Although the mechanism of action of gemfibrozil to improve clinical outcomes in patients with hypoalphalipoproteinemia has not been proven to be related to the increase in HDL-C (44), it is intriguing to speculate on the potential dramatic reduction in cardiac morbid events that may be achieved with combination gemfibrozil and NA therapy, on the basis of the clearly superior lipid profile with which the combination is associated. Although myositis and rhabdomyolysis were not observed in this small series, caution must be exercised when using this combination of agents, individualizing therapy where potential benefit may outweigh the risks of treatment (54).

By enhancing transcription of lipoprotein lipase, gemfibrozil appears to increase the catabolism of triglyceride-rich lipoproteins, resulting in an increased transfer of surface constituents to nascent HDL. In contrast to patients with type IV hyperlipoproteinemia, in whom there appears to be increased Apo A1 synthesis, in patients with isolated hypoalphalipoproteinemia, serum Apo A1 levels remain unchanged, suggesting either a lack of anabolic effect or a balanced increase in Apo A1 catabolism. The reduction in LDL-C and Apo B reported here with NA therapy is consistent with a decrease in VLDL particle synthesis (55). In the current series of patients, the increase in HDL-C and Apo A1 with NA therapy may occur largely by triglyceride-independent mechanisms. The lack of correlation between HDL-C increase and triglycerides decrease with NA therapy, as well as the greater increase in HDL-C with NA as compared with gemfibrozil therapy, despite the greater decrease in triglycerides with use of gemfibrozil, is consistent with this hypothesis. Measured lipid values suggest an additive effect of these two agents in patients with isolated hypoalphalipoproteinemia, consistent with their different postulated mechanisms of action.

Because ~40% of patients could not tolerate one or both of the pharmacologic agents used, data are presented using an "on-treatment" as opposed to "intention-to-treat" analysis. To perform the latter would merely serve to dilute the results and create the false impression that drug therapy, even when effectively delivered, is of no value for patients with isolated hypoalphalipoproteinemia.

Study limitations. The number of patients studied, although relatively small, is consistent with those in previously reported crossover trials of pharmacologic lipid-lowering agents and is adequately powered by using appropriate statistical methods to disprove multiple null hypotheses.

Although there was no true placebo group, it was hoped that this effect would be minimized somewhat by the crossover design of the trial. The study was nonblinded and lacked objective measures to assess drug compliance. However, the frequent doctor–patient encounters during follow-up, as well as the excellent agreement between baseline and final washout lipid profiles and their significant differences from those values obtained during treatment, suggest that reasonable drug compliance was achieved in most cases.

Conclusions. A large body of epidemiologic data suggests that low levels of HDL-C are strongly associated with an increased risk of CAD. Results from the VA-HIT mega-trial suggest that pharmacotherapy designed specifically to raise HDL-C in a group of patients with CAD and hypoalphalipoproteinemia and an otherwise unremarkable lipid profile can result in a significant decrease in subsequent morbid events from ischemic heart disease. Enrollment of patients in the randomized, double-blind, placebo-controlled Bezafibrate Infarction Prevention (BIP) (56) secondary prevention trial has been completed and results are pending.

The current study suggests that combination gemfibrozil and NA therapy in patients with isolated hypoalphalipoproteinemia can result in dramatic improvement of the lipid

profile—superior to that of either agent alone—in the majority of patients in whom drug treatment can be tolerated. Although some investigators have advocated such therapy (54,57), others have recommended treatment with reductase inhibitors to lower the already relatively "normal" LDL-C in these individuals, and thereby presumably decrease further the risk of atherosclerotic disease progression (46,48,58). To do so, however, may be akin to drilling a hole in the floor to drain water from a leak in the ceiling. Fixing the ceiling, if it could be accomplished safely, would seem a more logical approach.

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